

GUIDELINES ON RENAL CELL CARCINOMA

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Introduction

Renal cell carcinoma (RCC) represents 2–3% of all cancers; the highest incidence in Western countries. In Europe there is a general annual increase in incidence of around 2% (except in Denmark and Sweden). The use of imaging techniques such as ultrasound (US) and computerized tomography (CT) has led to an increase in the detection of RCC. Despite this increased incidental detection rate, mortality from RCC has stabilised, showing a tendency towards decline. The peak incidence occurs between 60–70 years of age, with a 1.5:1 ratio of men to women. Aetiological factors include lifestyle factors, such as smoking, obesity and therapy for hypertension. The most effective prophylaxis is to avoid cigarette smoking and obesity.

Diagnosis and classification

More than 50% of RCCs are diagnosed incidentally. Asymptomatic RCCs are generally smaller and of lower stage than symptomatic RCCs. Many RCCs remain asymptomatic and non-palpable until late in their natural course. The classic triad of flank pain, gross haematuria and palpable abdominal mass is seldom found (6–10%). Clinical symptoms include macroscopic haematuria, palpable mass, arising varicocele or

bilateral lower extremity oedema; these symptoms should initiate radiological examinations.

Paraneoplastic symptoms (e.g. hypertension, weight loss, pyrexia, neuromyopathy, anaemia, polycythaemia, amyloidosis, elevated erythrocyte sedimentation rate and abnormal liver function) are found in approximately 20–30% of patients with RCC. About 20–30% of patients with symptoms present as a result of metastatic disease.

Total renal function should always be evaluated. In patients with any sign of impaired renal function, a renal scan and total renal function evaluation should be undertaken to optimise the treatment decision.

Staging system

The UICC 2002 TNM (Tumour Node Metastasis) classification is recommended for the staging of RCC.

Table 1: The 2002 TNM staging classification system

T	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney
T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension
T2	Tumour > 7 cm in greatest dimension, limited to

the kidney

T3 Tumour extends into major veins or directly invades adrenal gland or perinephric tissues but not beyond Gerota's fascia

T3a Tumour directly invades adrenal gland or perinephric tissues¹ but not beyond Gerota's fascia

T3b Tumour grossly extends into renal vein(s)² or its segmental branches, or the vena cava below the diaphragm

T3c Tumour grossly extends into vena cava or its wall above the diaphragm

T4 Tumour directly invades beyond Gerota's fascia

N Regional lymph nodes³

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single regional lymph node

N2 Metastasis in more than one regional lymph node

M Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

¹ Includes renal sinus (peripelvic) fat

² Includes segmental (muscle-containing) branches

³ pN0 lymphadenectomy specimens will ordinarily include 8 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

A help desk for specific questions about TNM classification is available at <http://www.uicc.org/tnm>.

Histopathological classification

Fuhrman nuclear grade is the most commonly used grading system. The most aggressive pattern defines the Fuhrman grade. RCC comprises four genetically different subtypes: conventional (clear cell) (80–90%), papillary (10–15%), chromophobe RCC (4–5%), and collecting duct carcinoma (1%). In general, the RCC types have different clinical courses and responses to therapy. The Fuhrman grading and RCC subtype classification are recommended. Several integrated prognostic systems and nomograms, combining dependent prognostic factors, have been developed. These nomograms can be useful for predicting survival and differentiating follow-up.

Radiological investigations of RCC

Radiological investigations of RCC should include a high-quality CT scan, using contrast medium, to verify the diagnosis and provide information on the function and morphology of the contralateral kidney and assess tumour extension, including extrarenal spread, venous involvement, and enlargement of lymph nodes and adrenals. Abdominal US and especially magnetic resonance imaging (MRI) are alternatives to CT. MRI can be reserved for patients with possible venous involvement, renal insufficiency or allergy to intravenous contrast. Chest CT is the most accurate chest staging; a routine chest X-ray should be done as a minimum.

Only if indicated by clinical symptoms or laboratory signs should other diagnostic procedures be considered in selected cases. These procedures include bone scan, MRI, brain CT, renal arteriography, and inferior venacavography. Fine-needle biopsy has only a limited role in the clinical work-up of

patients with renal masses.

Guidelines for the primary treatment of RCC

Until recently, complete removal of RCC was the gold standard for curative therapy for localized RCC. For smaller RCCs, nephron-sparing surgery is recommended, and radical nephrectomy is no longer the standard of care. There is no evidence favouring a specific surgical approach, although laparoscopic radical nephrectomy is considered a standard of care for T1b-2 RCCs.

If the preoperative CT scan is normal, routine adrenalectomy is not recommended. Lymphadenectomy should be restricted to staging as extended lymphadenectomy does not improve survival. In patients who have RCCs with tumour thrombus and no metastatic spread, prognosis is improved after nephrectomy and complete thrombectomy.

Embolisation of the primary tumour is indicated in patients with gross haematuria or local symptoms (e.g. pain), in patients unfit for surgical intervention, and before surgical resection of large skeletal metastases. No benefit is associated with tumour embolisation before routine radical nephrectomy.

Nephron-sparing surgery

Absolute indications for partial nephrectomy are anatomical or functional solitary kidney or bilateral RCC. Relative indications are a functioning opposite kidney affected by a condition that might impair renal function and hereditary forms of RCC with high risk of developing a tumour in the contralateral kidney. Localized unilateral RCC with a healthy contralateral kidney is

an indication for elective surgery.

Nephron-sparing surgery is recommended for patients with tumours ≤ 4 cm, as recurrence-free and long-term survival rates are similar to those associated with radical nephrectomy. Even in selected patients with a tumour diameter up to 7 cm nephron-sparing surgery has achieved results equivalent to those observed after a radical approach; however, it is not recommended as a standard procedure. If the tumour is completely resected, the thickness of the surgical margin (> 1 mm) does not correlate with the likelihood of local recurrence. If RCCs of larger size are treated with nephron-sparing surgery, follow-up should be intensified as there is an increased risk of intra-renal recurrences.

Laparoscopic nephrectomy

Laparoscopic radical nephrectomy has a lower morbidity compared with open surgery. The laparoscopic approach allows early control of the renal vessels before tumour manipulation, wide specimen mobilization external to Gerota's fascia, avoidance of specimen damage or rupture and intact specimen extraction. Laparoscopic radical nephrectomy is recommended as a standard of care for patients with T1b-2 RCCs, and outcome data indicate that cancer-free survival rates are equivalent to those achieved using open radical surgery. Laparoscopic nephrectomy is expected to become a widely available treatment option and should be promoted in centres treating RCC.

Partial laparoscopic nephrectomy might be an alternative to open surgery for selected patients in experienced hands.

The optimal indication for partial laparoscopic nephrectomy is a relatively small and peripheral renal tumour. Although the oncological outcome following laparoscopic partial nephrectomy has been suggested to duplicate that of open techniques, reliable long-term data from large studies are not available. Disadvantages of the laparoscopic approach are the longer warm ischaemia time and increased intra-operative and post-operative complications compared with open surgery.

Open partial nephrectomy remains the standard of care. Laparoscopic partial nephrectomy should be limited to experienced centres.

Minimally invasive alternative treatment

Minimally invasive techniques, for example percutaneous radio-frequency (RF), cryotherapy, microwave, and high-intensity focused US ablation (HIFU) are suggested alternatives to surgery. Potential advantages of these techniques might include reduced morbidity, outpatient therapy and the ability to treat high-risk patients not fit for conventional surgery.

Table 2: Primary surgical treatment of RCC according to T stage

T1a	Nephron-sparing surgery	Open	
		Laparoscopic	
	Radical nephrectomy		
T1b-T2	Radical nephrectomy	Open	
		Laparoscopic	
	Nephron-sparing surgery		
T3,T4	Radical nephrectomy	Open	
		Laparoscopic	

These experimental treatments might be recommended for selected patients with small, incidentally found, renal cortical lesion, elderly patients, patients with a genetic predisposition to multiple tumours, patients with a solitary kidney, or patients with bilateral tumours. The oncological success rate and complications after these procedures have to be defined within clinical trials.

Adjuvant therapy

Adjuvant tumour vaccination might improve the duration of the progression-free survival, especially in patients with T3 RCC. Cytokine therapy does not improve survival after nephrectomy. Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.

Surgical treatment of metastatic RCC (mRCC)

Nephrectomy of the primary tumour is curative only if surgery can excise all tumour deposits. For most patients with mRCC, nephrectomy is only palliative. In a meta-analysis of two randomized studies, comparing nephrectomy combined with

	Recommended standard
	Optional in experienced centres
	Reasonable in selected patients
	Adequate and recommended but with a higher morbidity
	Recommended standard
	Feasible in selected patients in experienced centres
	Recommended standard for most patients
	Feasible in selected patients

immunotherapy versus immunotherapy alone, increased long-term survival was found in patients who underwent nephrectomy. In patients who have a good performance status tumour nephrectomy, in combination with interferon-alpha (IFN- α) treatment, can be recommended.

Complete removal of metastases contributes to improved clinical prognosis. In patients with metastatic spread, metastasectomy should be carried out in cases with resectable disease and a good performance status. Metastasectomy should also be considered in patients with residual and respectable metastatic lesions previously responding to immunotherapy.

Radiotherapy for metastases

For selected patients with non-resectable brain or osseous lesions radiotherapy can induce significant symptom relief.

Systemic therapy for mRCC

Chemotherapy

Chemotherapy is considered ineffective in patients with RCC.

Immunotherapy

Available data show that immunotherapy with IFN- α is beneficial for only a limited subset of patients; those with a good performance status, a progression-free survival of > 1 year following initial diagnosis, and preferably lung metastasis as the sole metastatic site. All recent randomized studies comparing anti-angiogenic drugs in a first-line setting to IFN- α monotherapy have demonstrated superiority for either sunitinib, bevacizumab + IFN- α or temsirolimus. IFN- α monotherapy is

not longer recommended as first-line therapy for mRCC.

High-dose bolus interleukin-2 (IL-2) gives durable complete responses in a limited number of patients, however, the toxicity associated with IL-2 is substantially higher than that with IFN- α . To date, no superiority has been seen for treatment with either IFN- α or IL-2 treatment in mRCC patients. Only patients with clear cell subtype histology benefit clinically from immunotherapy with IL-2.

A combination of cytokines with, or without, additional chemotherapy does not improve overall survival compared with monotherapy.

Angiogenesis inhibitor drugs

Vascular endothelial growth factor (VEGF) and tyrosine kinase inhibitors have shown efficacy in clear cell RCC. Tyrosine kinase inhibitors increase progression-free survival as both first- and second-line treatment of mRCC.

- Sorafenib is an oral multikinase inhibitor and has proven efficacy as second-line treatment after failure of systemic immunotherapy.
- Sunitinib is an oral tyrosine kinase inhibitor. In a phase III first-line study comparing sunitinib with IFN- α , sunitinib achieved a longer progression-free survival time (11 months versus 5 months) in low- and intermediate-risk patients. In patients who did not receive any post- study treatment, overall survival was longer in the sunitinib only treated group than in the IFN- α only group (28.1 months versus 14.1 months, respectively).
- Bevacizumab is a monoclonal antibody that binds VEGF-A.

A double-blind placebo controlled phase III trial investigated the addition of IFN- α to bevacizumab. In low- and intermediate-risk patients, the median progression-free survival significantly increased from 5.4 months with IFN- α alone to 10.2 months with bevacizumab + IFN- α .

- Temsirolimus is a specific inhibitor of mammalian target of rapamycin. A phase III trial demonstrated increased overall survival in poor-risk patients with mRCC on temsirolimus monotherapy compared with IFN- α .
- Everolimus is an oral mTOR inhibitor. A recent phase III study in patients who had failed previous anti-VEGF-R treatment showed a progression-free survival of 4 months with everolimus versus 1.9 months with placebo.

The position of these and other new novel agents, as monotherapy, in combination or in the adjuvant setting, for the treatment of primary or secondary treatment of mRCC, is under investigation. No overall survival data are available for any of these new agents.

Recommendations for systemic therapy

Tyrosine kinase inhibitors should be considered as first- or second-line treatment for mRCC patients as shown in Table 3.

Table 3: Recommendations for first- and second -line systemic therapy in mRCC

Treatment	Risk or prior treatment	Recommended agent
• First- line therapy	Low- or intermediate- risk	- Sunitinib - Bevacizumab + IFN- α

	High risk	Temsirolimus
• Second- line therapy	Prior cytokine	Sorafenib
	Prior VEGFR Prior mTOR(-)	Everolimus Clinical trials

Surveillance following surgery for RCC

Surveillance following surgery for RCC allows the urologist to monitor postoperative complications, renal function, local recurrence, recurrence in the contralateral kidney and development of metastases. The main reason for identifying metastases early is to enhance the possibility of surgical resection and efficacy of systemic treatment when the tumour burden is as low as possible. There is no general recommendation on the method and timing of investigations for surveillance. Using different scoring systems and algorithms, patients can be categorized as low-, intermediate- or high-risk of developing metastases. The urologist can therefore be selective in the use of imaging and the need for intensive surveillance. There are no evidence-based standard for the follow-up of patients with RCC.

Table 4: Example of a follow-up regimen in mRCC

(NB: This is not an EAU follow-up recommendation)

Low-risk patients (pT1a N0 M0 G1-2)	Clinical follow-up, surveillance with annual chest X-ray, without routine CT. But surveillance may also be omitted due to few events
Intermediate-risk patients (pT1b-2 N0 M0, and pT1a N0 M0G3-4) ally	Surveillance with CT of the thorax or chest X-ray every 6 months for 2 years and annually for 5 years

High-risk patients (all pT3-4 N1-2 M0)	More intensive follow-up with CT of the abdomen and the chest at 3 months, every 6 months for 2 years and thereafter annually for 5 years.
Metastatic disease	Individual follow-up plan required

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-09-0), available to all members of the European Association of Urology at their website - <http://www.uroweb.org>.